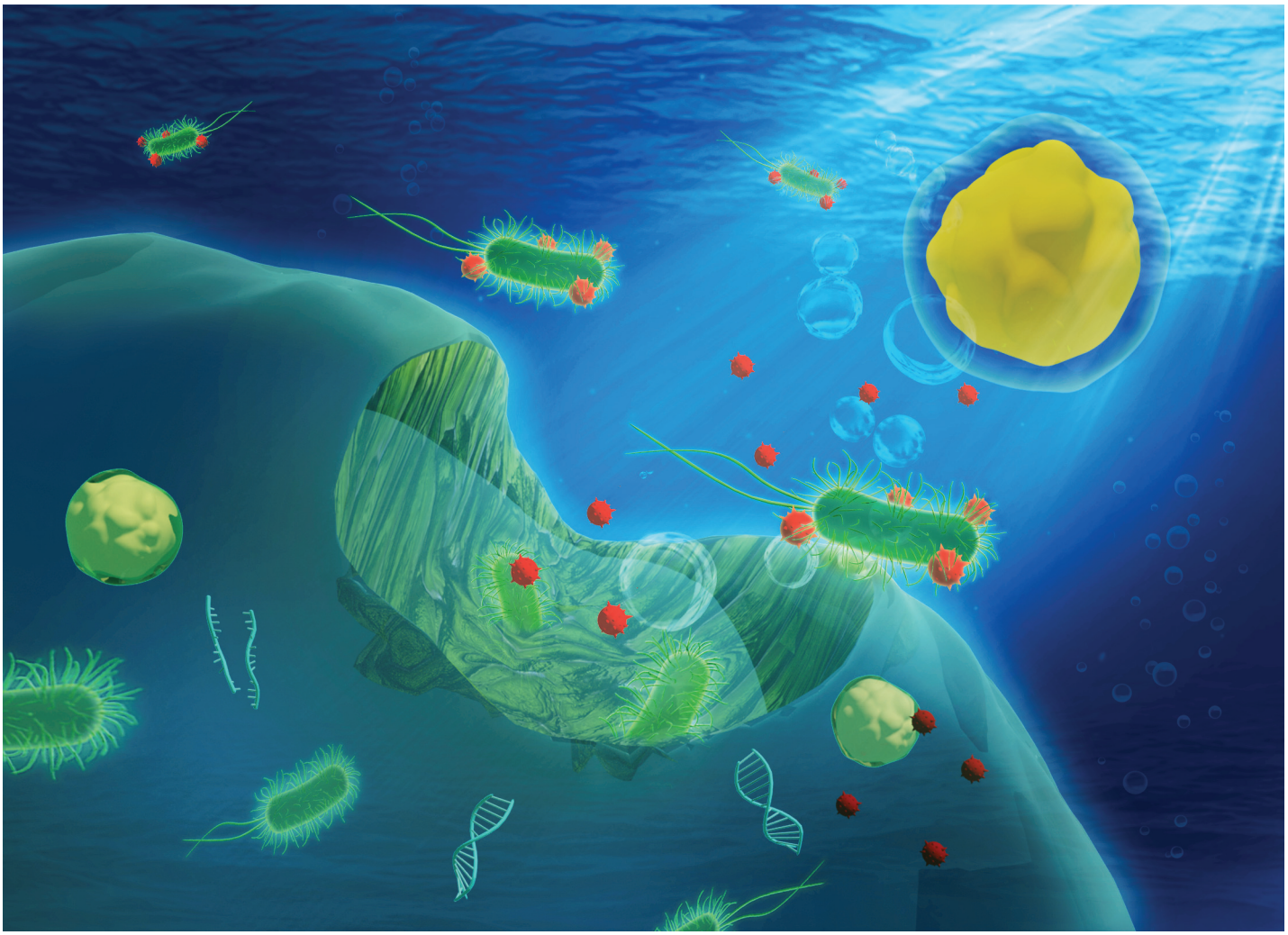

Showcasing research from Professor Lin's laboratory, Xiamen University, Xiamen, China.

Recent advances in nanoparticulate biomimetic catalysts for combating bacteria and biofilms

Due to the abuse of antibiotics and the tendency of bacteria to form protective biofilms, the development of new agents that can eliminate bacteria and biofilms is highly desired. Among them, nanomaterials with enzyme-mimetic activities (nanozymes) are considered as suitable candidates. This review summarizes the recent progress of nanozymes in this highly active field, including their antibacterial mechanisms, key factors that affect their overall performance, and the current challenges and prospects. We expect this active research area will continue to thrive and mature in the future.

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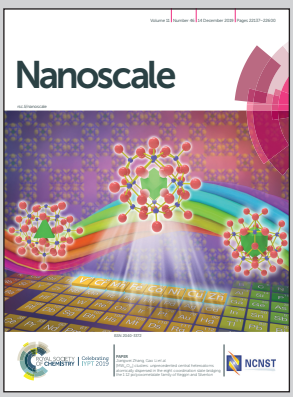

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Recent advances in nanoparticulate biomimetic catalysts for combating bacteria and biofilms

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Due to the abuse of antibiotics and the tendency of bacteria to form protective biofilms, the design and development of new efficient agents that can eliminate bacteria and biofilms are still highly desired but remain a great challenge; on the other hand, natural enzymes with unique catalytic characteristics can cause an irreversible damage to the bacteria without inducing drug-resistance in the bacteria. However, the intrinsic drawbacks, such as insufficient stability and high purification cost, of enzymes significantly limit their antimicrobial applications. Therefore, significant research efforts have been devoted towards the development of quality-equivalent or even superior enzyme substitutes with low cost and high stability. In this regard, nanomaterials with extraordinary enzyme-mimetic catalytic activities (termed as nanozymes) are considered as suitable candidates. To date, nanozymes have been proved to be promising materials for combating bacteria and biofilms under mild conditions. In this review, we have summarized the recent progress of nanozymes in this highly active field. The antibacterial mechanisms of nanozymes and the roles of their sizes, morphologies, compositions, surface modifications and microenvironment on their overall performance have been discussed. Moreover, the current challenges and prospects in this research area have been discussed. We believe that nanozymes with unique features and functions can provide a wealth of opportunities *via* their clinical and industrial applications.

Bacterial infection, one of the primary causes of morbidity and death, is a global problem that humankind must solve. To date, antibiotics have been widely and frequently used for the treatment and prevention of these infections. However, the abuse of antibiotics has prompted the emergence of drug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (*S. aureus*). Bacteria can adapt or become resistant to antibiotics *via* a variety of ways such as by inactivating the enzyme, decreasing the cell permeability, changing the target site, and increasing the efflux;[1] therefore, due to the increasingly serious antibiotic resistance of pathogenic bacteria, it has become difficult to combat them.[1] Moreover, biofilm is a community of bacteria with close communication in a matrix of extracellular polymeric substances (EPS). In addition, biofilms can hold the bacteria together and form recalcitrance to treatment by antibacterial agents;[1] therefore, the design and development of new and efficient antimicrobial agents is still a key challenge. Recent advances in nanoscience and nanotechnologies have provided opportunities for the use of nanomaterials as components towards the development of antibacterial and antibiofilm agents: (1) nanostructured materials can be used as nanocarriers to achieve efficient delivery of antimicrobials or drugs;[2–4] (2) many nanomaterials themselves possess intrinsic antibacterial and antibiofilm activities;[5,6] and (3) due to the intrinsic antibacterial potential or other special properties of nanomaterials, their presence can help the formation of synergistic systems that combine two or more antimicrobial agents or the construction of smart on-demand therapeutic modalities.[7,8] To date, many nanomaterials with antibacterial activities have been well investigated to kill bacteria.[1,7–11] The widely explored Ag nanoparticles, for example, have been reported to have good antibacterial activity, which is mainly because of the release of Ag^+ that triggers the production of intracellular reactive oxygen species (ROS) and thus causes the lysis of a broad spectrum of bacteria;[12] although these nanoparticles are promising, their inherent cytotoxicity limits their development.[12] In addition,

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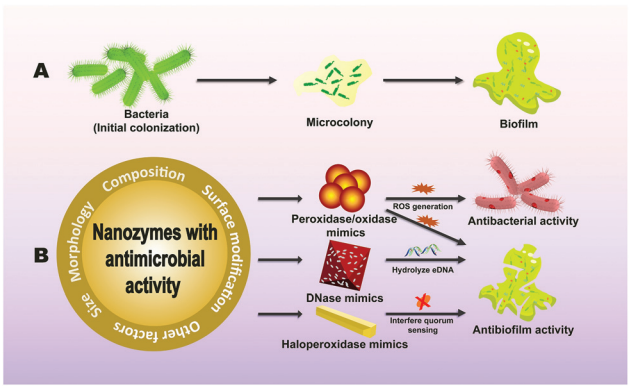
some photocatalysts can serve as antibacterial agents by photo-catalytically causing oxygen reduction and generating reactive oxygen species such as $^{\bullet}O^{2-}$ and H_2O_2.[13,14] Recently, nanomaterials with enzyme-like activities have also been discovered to combat bacteria and biofilms. These catalytically active nanomaterials are also termed as nanozymes.[1] The use of nanozymes as antimicrobial agents takes inspiration from nature.

In living systems, some natural self-defense systems exist that utilize biocatalysts to irreversibly damage the bacteria or disrupt the biofilm integrity. For example, peroxidase and oxidase in lysosomes can catalyze the generation of ROS to combat bacterial invasion. However, natural enzymes often suffer from inherent shortcomings such as high cost and poor stability. Recently, tremendous efforts have been devoted towards the construction of nanozymes[15–19] including metal-, metal oxide-, sulfide metal-based nanomaterials,[20–23] carbon-based nanomaterials,[24] and nano-hybrids.[25,26] Compared with natural enzymes, nanozymes are cost-effective and more sustainable. Moreover, these nanoparticulate biomimetic catalysts as antimicrobial agents show good biocompatibility under the dosage needed to achieve an effective clinical outcome, special chemical and physical properties (*e.g.*, optical, electronic, and magnetic properties), tunable surface properties, and ease of functionalization for enhancing the antibacterial efficiency. These unique properties may offer a possibility for the development of novel multifunctional antimicrobials. Recently, the utilization of nanozymes in fighting multi-drug resistant bacteria and biofilms has become a hot research area.[27–29]

Although many excellent studies have been reported in this regard, to the best of our knowledge, no comprehensive review has been devoted towards the current progress. Herein, this review provides an update on the recent developments of these nanoparticulate biomimetic catalysts in combating bacteria and biofilms. The antibacterial mechanisms and the roles of their sizes, morphologies, compositions, surface modifications, and microenvironment on their overall performance have also discussed in this review (Scheme 1). Furthermore, the current challenges and prospects of nanozymes in this area have been discussed. We hope that the introduction of nanozymes can broaden the research fields of combating bacteria and biofilms and enlarge the range of new possibilities for catalytically active nanomaterials.



Scheme 1 Schematic of the biofilm formation model and nanoparticulate biomimetic catalysts for combating bacteria and biofilms.

The antibacterial mechanisms of nanozymes

To date, many nanozymes have been discovered to possess intrinsic antibacterial and antibiofilm activities (Table 1). Although the mechanisms of these unexpected activities have not been thoroughly studied and fully understood, they mainly involve the following three aspects:

(1) The generation of highly active ROS products by redox nanozymes. Most of the antibacterial activities of nanozymes originate from their ability to modulate the level of ROS such as hydroxyl radical ($^{\bullet}OH$) and superoxide anion ($O_2^{\bullet-}$).[30] Owing to their high oxidation capability, ROS can attack bacteria and biofilms and unselectively defunctionalize many biomolecules such as lipids, proteins and nucleic acids, leading to the disruption of the bacterial cytoplasmic membrane, DNA damage, and protein deactivation. Moreover, it is difficult for the bacteria to develop resistance to these antimicrobials as they cause membrane destruction; therefore, by increasing the level of ROS, the bacteria may be quickly and efficiently killed.[14,31,32]

As is known, H_2O_2 alone can serve as a common antibacterial agent. To achieve good antibacterial performance, a relatively higher concentration of H_2O_2 (0.5–3%) is often needed.[33] However, healthy tissues may also be affected when exposed to this high level of H_2O_2.[32,33] Fortunately, the presence of peroxidase-like nanozymes can decompose H_2O_2 into the highly oxidative $^{\bullet}OH$.[33,34] In this way, a much lower concentration of H_2O_2 is needed to achieve higher antibacterial efficacy, which is more friendly to the organism. We observed that the formation of $^{\bullet}OH$ by peroxidase-like nanozymes might depend on their types. For gold nanoparticle-based peroxidase mimics, H_2O_2 can be adsorbed on the surface of gold nanomaterials, and then, the O–O bond of H_2O_2 may be broken into double hydroxyl radicals.[35] In addition, nanomaterials with oxidase-like activity can modulate the level of ROS by catalytically producing $^{\bullet}O_2^-$ from oxygen. In this way, the supply of H_2O_2 is no longer necessary to exert antibacterial effects.[36]

(2) The cleavage of extracellular DNA (eDNA) by hydrolytic nanozymes. eDNA is one of important EPS constituents for many bacterial species and has a very significant role in maintaining the biofilm integrity.[16,37] Deoxyribonuclease (DNase) mimics can cleave eDNA to inhibit the formation of biofilms and disperse the established biofilms.

(3) The interference of quorum sensing by haloperoxidase mimics. Haloperoxidase mimics that can quench auto-inducers (small molecules related to quorum sensing) have been reported to successfully prevent biofilm growth and disrupt biofilms.[38]

Table 1 Enzyme-mimetic nanoparticles against pathogens

Types of nanoparticles	Enzyme-mimetic activities	Antibacterial mechanisms	Targets
Single atom nanzozyme[39]	Peroxidase-like activity	Generation of $^{\bullet}OH$	*P. aeruginosa*
o-CNTs[40]	Peroxidase-like activity	Generation of $^{\bullet}OH$	*S. aureus*, *E. coli*
Modified CuO nanorods[41]	Peroxidase-like activity	Generation of $^{\bullet}OH$	*E. coli*
Graphene quantum dots[38]	Peroxidase-like activity	Generation of $^{\bullet}OH$	*S. aureus*, *E. coli*
AuDAMP[23]	Peroxidase- and oxidase-like activity	Generation of $^{\bullet}OH$ and $^{\bullet}O_2^-$	*E. coli*, *A. baumannii*, *P. aeruginosa*, MRSA, MDR *K. pneumoniae*, VRE
Pt hollow nanodendrites[42]	Peroxidase- and oxidase-like activity	Generation of $^{\bullet}OH$ and $^{\bullet}O_2^-$	*S. aureus*, *E. coli*
GQD/AgNP hybrids[36]	Peroxidase- and oxidase-like activity	Generation of $^{\bullet}OH$ and $^{\bullet}O_2^-$	*S. aureus*, *E. coli*
Mesoporous Silica-Supported gold Nanoparticles[38]	Peroxidase- and oxidase-like activity	Generation of $^{\bullet}OH$ and $^{\bullet}O_2^-$	*S. aureus*, *E. coli*
Porous Pt/Ag nanoparticles[38]	Peroxidase- and oxidase-like activity	Generation of $^{\bullet}OH$ and $^{\bullet}O_2^-$	*S. aureus*, *E. coli*
PEG-MoS_2 nanoflowers[32]	Peroxidase-like activity	Combination of the generation of $^{\bullet}OH$ and photothermal therapy	*E. coli*, *B. subtilis*
CaO_2/H-G@alginate[43]	Peroxidase-like activity	Generation of $^{\bullet}OH$ in cascade reaction	*S. aureus*, *E. coli*
IOPs[44]	Peroxidase-like activity	Combination of the generation of $^{\bullet}OH$ and the antibiotic methicillin	Biofilms
DMAE[45]	DNase-like activity	Multivalent Ce^{IV} center for hydrolyzing eDNA	Biofilms
$MOF_{-2.5Au-Ce}$[46]	DNase- and peroxidase-like activity	Multivalent Ce^{IV} center for hydrolyzing eDNA, generation of $^{\bullet}OH$	Biofilms
V_2O_5 nanowires[38]	Haloperoxidase-like activity	Generation of HOBr for the bromination of the signal molecules	Biofilms
CeO_{2-x} nanorod[47]	Haloperoxidase-like activity	Generation of HOBr for the bromination of the signal molecules	Biofilms

A single antibacterial system based on nanozymes

The ongoing accumulation and continuous innovation of nanozyme systems have enabled the nanozymes to control the bacterial infection. As catalysts, the activities of nanozymes are affected by many factors such as their sizes, morphologies, compositions, surface modification and microenvironment. Thus, an enhancement in the activity of nanozymes may lead to better antimicrobial performance.

Based on the important influence of size on the activity of nanozymes as well as the better penetration of ultrasmall-sized nanozymes into bacterial cells, Wang *et al.* have demonstrated that ultrasmall mercaptopyrimidine-conjugated gold nanoclusters exhibit excellent oxidase- and peroxidase-like activities and induce the generation of intracellular ROS after their entry. Compared with 6 nm gold nanoparticles, the obtained gold nanoclusters possessed significantly higher antibacterial activity. Especially, 4,6-diamino-2-mercaptopyrimidine-conjugated Au NCs (AuDAMP) exhibited superior antibacterial effects on both Gram-positive and Gram-negative bacteria than other mercaptopyrimidine-conjugated Au NCs. As illustrated in Fig. 1, the highly positively charged AuDAMP could electrostatically adsorb on the surface of the bacteria and destruct the cell membrane; this led to its efficient internalization. In this way, AuDAMP with oxidase- and peroxidase-like activities could induce a dramatic increase in the intracellular ROS level, accelerating the death of bacteria. A mouse skin infection model was further designed to value their potential biological application. Moreover, the experimental data demonstrated wound healing and 99% antibacterial efficacy with treatment

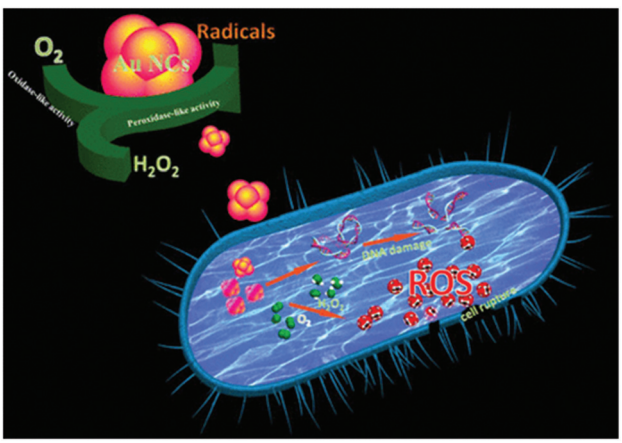


Fig. 1 Schematic of Au NCs as an antibacterial agent with oxidase- and peroxidase-like catalytic properties. Reprinted with permission from ref. 23. Copyright ACS 2018.

using AuDAMP (0.1 mL, 10 μg mL^{-1}) after 10 days.[23] Moreover, a recent study has reported that single-atom nanozymes, ZIF-8-derived carbon nanomaterials, within which unsaturated Zn–N_4 sites have been atomically dispersed, has a high peroxidase-like activity to catalytically decompose H_2O_2 into $^{\bullet}OH$. The generated $^{\bullet}OH$ exerted outstanding property of attacking the bacteria. This enzyme-like catalytic activity might be attributed to the unsaturated Zn–N_4 active sites in these single atom nanozymes where H_2O_2 was absorbed, activated and then decomposed. In the presence of the single-atom nanozymes and a low dosage of H_2O_2 (100 μM), up to 99.87% of *P. aeruginosa* growth could be prevented. Moreover, the wound

infection model further illustrated that with the assistance of the nanozymes and H_2O_2, the wound could completely heal after 6 days. This study contributed to the advancement of single-atom catalysts for biological applications.[39]

Modulation of the morphology can change the contact area with the substrates and the utilization of active sites, which is bound to dramatically impact the activity. Using various synthesis methods, nanomaterials with numerous morphologies, including rod, sheet, cage, and needle, have been developed. For example, Ge *et al.* have synthesized Pt hollow nanodendrites through chemical deposition and etching. They have reported that the obtained hollow nanodendrites can exhibit higher peroxidase-like activity than the Pd@Pt core-frame nanodendrites. This might be due to the high-index facets of the Pt branches and more exposure of the active sites. Moreover, the Pt hollow nanodendrites possessed oxidase-like activity, which was further beneficial to achieve higher antibacterial property. In the presence of 10 μM H_2O_2, the Pt hollow nanodendrites could kill *S. aureus* and *Escherichia coli* (*E. coli*) with the general lethality of 71.9%. Moreover, the experimental data of the mouse model showed that a bio-safe dosage of the nanozyme with relatively low concentration of H_2O_2 could work well in wound disinfection.[42]

More interestingly, metal- or inorganic-based nanohybrids have also attracted researchers' attention because the interaction between different components can offer the possibility of creating novel or superior properties. Recently, Chen and coworkers have successfully designed a graphene quantum dot/Ag nanoparticle (GQD/AgNP). Due to the synergistic effect between different components, the hybrids could exhibit not only an enhanced oxidase-like activity arising from the AgNPs, but also a higher peroxidase-like activity due to the faster electron transfer and reduction of –C–OH on the GQD. When bacteria were treated with GQD/AgNP hybrids (2 μg mL^{-1}), only 33% of *S. aureus* and 18% of drug-resistant *E. coli* survived. On the contrary, the commercial antibiotics ampicillin and amoxicillin showed little antibacterial efficacy even at the concentration of 100 μg mL^{-1}. Further studies have demonstrated that with the addition of H_2O_2 or the introduction of photodynamic therapy, the antibacterial efficacy would be enhanced; based on these observations, it has been confirmed that nanohybrids can efficiently generate ROS and thus exhibit excellent antibacterial activity against bacteria.[36]

In addition to the regulation of size, morphology, and compositions as abovementioned, surface modification, microenvironment adjustment,[16] and application of external power[41] are feasible strategies to improve the antibacterial effects of nanozymes. To date, surface modification has been widely applied to endow multiple functions and improve the properties of nanozymes. For example, some polymers, such as chitosan, can act as stabilizers of AgNPs to prevent their aggregation and improve their stability.[48] In addition, biotics, such as vancomycin, can be coupled to some metal nanoparticles for targeting a wide range of bacteria.[49] These surface modification methods would be beneficial for the performance of antibacterial agents. For example, since the carbonyl groups on carbon nanotubes are active sites for their peroxidase-like activity, whereas the carboxyl groups and hydroxyl groups are the competitive sites, the oxygen-group-enriched carbon nanotubes (o-CNTs) can be modified to have higher peroxidase-mimetic activity by blocking the carboxyl groups. The modified o-CNTs were proved to demonstrate improved antibacterial effects when employed in disinfection.[40] External power, such as light, can also be a tool to modulate the enzyme-like activities of some nanoparticles.[50] CuO nanorods (CuO NRs), designed to possess appropriate energy-band structures, were reported to show enhanced peroxidase-like activity when exposed to visible light. In this study, the synthesized p-type semiconducting CuO NRs had typical narrow band gaps that allowed the nanorods to absorb visible light. When they were activated under light illumination, their affinity to H_2O_2 was over 4 times that of the unilluminated nanorods, resulting in 20 times enhancement in the $^{\bullet}OH$ production rate (Fig. 2A). As shown in Fig. 2B, under light illumination, more $^{\bullet}OH$ species were generated when compared with the case of the dark condition, causing severe damage to bacteria with the same dosage of H_2O_2.[41] This light-tuning-activity method might introduce a highly attractive way to trigger on-demand antibacterial function.

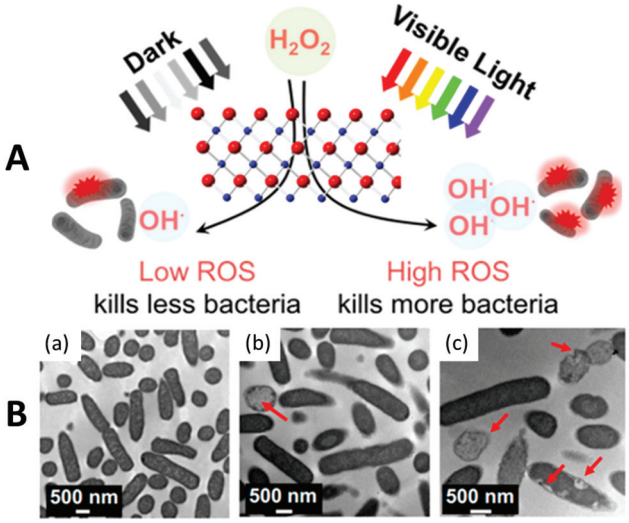


Fig. 2 Antibacterial performance of the CuO NRs under visible light illumination. (A) Schematic of antibacterial efficacy based on the enzyme-like activity of CuO NRs; (B) representative TEM images of *E. coli* after different treatments: (a) untreated; (b) CuO NRs + H_2O_2 in the dark; (c) CuO NRs + H_2O_2 with visible light illumination. Reprinted with permission from ref. 41. Copyright ACS 2018.

Moreover, a recent report showed that the presence of histidine on the surface of Fe_3O_4 nanoparticles could enhance the intrinsic peroxidase-like activity of Fe_3O_4 nanoparticles. With the assistance of histidine, H_2O_2 could be accurately located in the active site cavity. It was proved that with similar size or morphology, histidine-modified Fe_3O_4 nanoparticles had a better affinity towards the substrates and higher peroxidase-like activity than naked-Fe_3O_4.[51] The key of this method was to use biocompatible alternatives to mimic the structures of

natural enzymes for enhancing the catalytic performance.[51,52] Inspired by this study, Wang *et al.* used poly (2-acrylamido-2-methyl-1-propane sulfonic acid)-based hydrogels to act as good carriers and offer Fe_3O_4 nanoparticles with better affinity to the substrates. By modulating the crosslinking concentration of the hydrogels, the affinity to H_2O_2 could be adjusted such that the peroxidase-mimetic activity of the Fe_3O_4 component was improved.[53] Overall, it is conceivable that by providing an appropriate microenvironment, the catalytic activity, such as oxidase- and peroxidase-like activity, of nanozymes can be greatly improved, leading to enhanced antibacterial performance.

A synergetic antibacterial system based on nanozymes

Nanozyme-based synergetic systems can also be applied for increasing the antibacterial efficiency and selectivity.[38] The use of sterilizing molecules, photothermal treatment and antibiotic delivery are promising strategies in this regard.[9,54,55] It is well established that organosulfur compounds, such as allicin, are main contributors to the antibacterial performance of garlic bulbs. However, for a single kind of organosulfur compounds, the instability and relatively poorer antibacterial effects limit their potential biomedical applications. To this end, recent studies have started to explore the possibility of nanoscale metal sulfides as antibacterial agents. Among them, nano-scale iron sulfides (nFeS) converted from organosulfur compounds (*e.g.*, cysteine, DADS, or DATS) have attracted researchers' attention. It was found that $cysteine_{0.5}$-nFeS, in which 0.5 g of cysteine was added in a total volume of 50 mL of the solvothermal system, could exhibit superior antibacterial efficacy and broader antibacterial performance. Their antibacterial effects can be several hundred times higher than those of garlic-derived organosulfurs; further studies have indicated that hydrogen disulfane and hydrogen trisulfane, which are released from the oxidative and nanostructural transformations on nFeS (Fig. 3A and B), respectively, are mainly responsible for the antibacterial efficacy of nFeS; this result is based on the fact that H_2S_2 and H_2S_3 can kill bacteria and disrupt the biofilm integrity efficiently. Moreover, H_2O_2 decomposition, catalyzed by the intrinsic peroxidase-like activity, could promote the oxidation of nFeS to accelerate the polysulfane release as well as increase the bacteria-killing efficacy of H_2O_2. The correlation of free sulfide release and the H_2O_2 concentration reflected from $OD_{340\ nm}$ (the absorbance at 340 nm that characterized free sulfide in the supernatant) in Fig. 3C further verified this conclusion. Wound healing in animal experiments also indicated the great potential of polysulfanes to combat bacteria and biofilms through the synergistic effect of the enzyme-like activity and catalysis-accelerated release of polysulfanes (Fig. 3D).[56]

Photothermal therapy is an attractive strategy that has recently been explored to be incorporated into nanozyme systems for antibacterial applications. During this therapy, abundant heat can be generated by the photo-absorbing

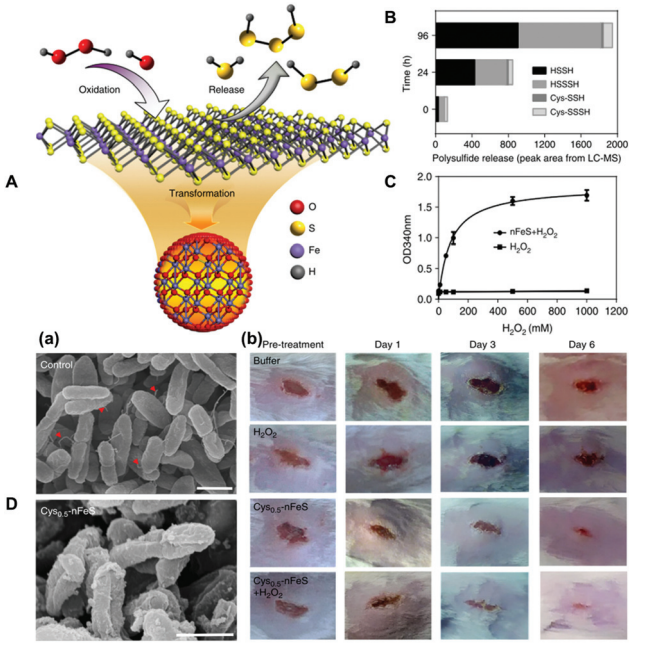


Fig. 3 The antibacterial activity of nFeS based on polysulfane release. (A) Schematic showing the polysulfane release from nFeS. (B) The ratio of different kinds of polysulfanes in the supernatant by LC–MS/MS. (C) Increase in polysulfane release driven by H_2O_2 *via* catalysis. (D) Sterilization and infected-wound healing using the nFeS regimen. Reprinted with permission from ref. 56. Copyright 2018 Nature Publishing Group.

agents under near-infrared (NIR) irradiation.[57] A previous study has proved that molybdenum disulfide (MoS_2) nanomaterials possess excellent peroxidase-like activity and high efficiency of NIR photothermal conversion. Inspired by these unique properties, Zhao, Gu, and coworkers have constructed polyethylene glycol-functionalized molybdenum disulfide nanoflowers (PEG-MoS_2 NFs) for antibacterial applications (Fig. 4A). The experimental data showed the concentration-dependent and NIR irradiation-promoted antibacterial performance of the PEG-MoS_2 NFs. As shown in Fig. 4B, a dramatic decrease in the bacterial viability was observed with an increase in the concentration of PEG-MoS_2 NFs. Moreover, under 808 nm NIR irradiation, the bacterial viability declined significantly. By combining the peroxidase-like capacity and photothermal property, the obtained PEG-MoS_2 NFs achieved almost 100% sterilization rate. The wrinkled morphology of the bacteria shown in the SEM images further proved the severe damage caused by the treatment of MoS_2–H_2O_2 with NIR irradiation (Fig. 4C).[32]

Although ROS is deadly to bacteria, the premise is that ROS efficiently acts on the targeted bacteria. In this way, accurate and controllable delivery becomes a vital point that needs careful consideration. To solve this problem, the introduction of the targeting effect can be a practical way.[4] Recently, Qu, Ren, and coworkers successfully designed a novel nanocomposite, where prodrug ascorbic acids were encapsulated in hyaluronic acid-dopamine conjugate-deco-

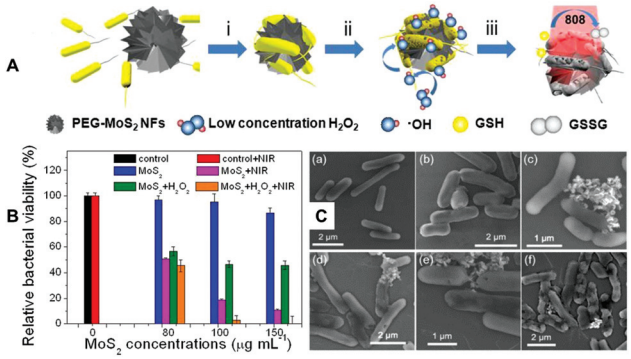


Fig. 4 Antibacterial performance of the PEG-MoS_2 NFs. (A) Schematic of the killing of bacteria by PEG-MoS_2 *via* a combination of peroxidase-like activity and photothermal treatment. (i) Bacteria were absorbed on PEG-MoS_2; (ii) PEG-MoS_2 catalyzed the formation of $^{\bullet}OH$ from the decomposition of a minimal amount H_2O_2 to damage the cell membrane integrity; (iii) PEG-MoS_2 released abundant heat under irradiation with a 808 nm laser, thus accelerating GSH oxidation. (B) The survival rate of *Ampr E. coli* after treatment with various concentrations of PEG-MoS_2 NFs with or without H_2O_2 when exposed to the 808 nm laser. (C) FE-SEM images of *Ampr E. coli* after different treatments. (a) PBS, (b) H_2O_2, (c) MoS_2, (d) MoS_2 + NIR, (e) MoS_2 + H_2O_2, and (f) MoS_2 + H_2O_2 + NIR. Irradiation time: 10 min. Reprinted with permission from ref. 32. Copyright ACS 2016.

rated graphene-mesoporous silica nanosheets. Vancomycin-modified ferromagnetic nanoparticles were then carried on them. As is well-known, vancomycin is a kind of antibiotics that can bind specifically to the amino acid residues of the glycanpeptidyl precursor on the bacterial cell wall to interfere with peptidoglycan synthesis, finally damaging and killing the bacteria.[58] Therefore, once vancomycin guided the nanoagents to the bacterial surface, the degradation of the hyaluronic acid–dopamine conjugates caused by bacteria could promote the release of ascorbic acids. In addition, ferromagnetic nanoparticles could catalytically induce ROS generation near the bacteria. Moreover, the excellent photothermal property of graphene further contributed to the sterilizing effects.[34]

Traditional nanozyme-based antibacterial systems require the supply of H_2O_2. However, a recent study has claimed that to realize great antibacterial efficacy, the additional administration of H_2O_2 is not necessary. In a system where CaO_2 and hemin-loaded graphene were integrated into alginate (CaO_2/H-G@alginate), CaO_2 could react with water to self-generate H_2O_2, which was, in turn, transformed into highly toxic $^{\bullet}OH$ with the assistance of hemin-loaded graphene. The results obtained after coincubating CaO_2/H-G@alginate with Gram-positive *S. aureus* and Gram-negative *E. coli* well evaluated the great germicidal activity of this system. The survival of *S. aureus* and *E. coli* decreased to 9.1% and 4.6%, respectively. Moreover, it was proved in the *in vivo* biofilm model that CaO_2/H-G@alginate could inhibit biofilm formation and destruct the biofilms, causing over 90% reduction of biomass after treatment for 24 h.[43] This nanozyme-based cascade system might open a new avenue for preventing bacterial infection in the absence of H_2O_2.

Nanozymes for combating biofilms

A biofilm, as a community where multiple microbial cells live in a complex matrix EPS, consists of many components such as proteins, polysaccharides, nucleic acids and other biomolecules.[59] The formation of a biofilm may involve three stages: the attachment of bacteria to the surface of the substrates for initial colony formation, the microcolony formation, and differentiation into a mature biofilm. Notably, some necessary quorum sensing molecules are responsible for regulating the growth of biofilms.[59–61] Biofilms are inherently recalcitrant to antimicrobials. On the one hand, it could be due to the failure of these antimicrobials to penetrate into the matrix. On the other hand, it has also been reported that intercellular communication can induce the quick response of microbes and regulate metabolism. Through this progress, microbes could adapt to the new environment quickly with improved resistance.[62] The formation of a biofilm provides a significant challenge to the sterilization and infection treatments. Therefore, it is urgent to develop novel and highly efficient agents for combating biofilms.

ROS, as strong oxidants, can destroy biofilms by destroying the important components and bacteria in the biofilm matrix. However, as the bacteria in biofilms are closely connected, ROS catalytically induced by nanozymes should have the capability of thoroughly destroying the entire biofilm such that biofilms do not regenerate. Moreover, good binding ability and activity retention within the biofilm are highly beneficial to the disruption of biofilms. To achieve this goal, catalytic nanoparticles containing Fe_3O_4 (CAT-NPs) were successfully constructed by the Koo's group. The CAT-NPs were able to well retain their peroxidase-like activities throughout the *S. mutans* biofilms and could penetrate the biofilms in depths ranging from 25 to 150 μm. Consequently, the generation of ROS *in situ* could realize the efficient disruption of the *S. mutans* biofilm, inhibiting the development of caries efficiently.[62] Similarly, ferumoxytol nanoparticles with peroxidase-like capacity were also found to be able to disrupt intractable biofilms and prevent dental caries.[63] Interestingly, this biocompatible nanomaterial with antibiotics together can be loaded into nanocarriers to realize cooperation in combating the biofilms. Polymersomes have been shown to co-encapsulate hydrophobic superparamagnetic iron oxide nanoparticles (SPIONs) and the hydrophilic antibiotic methicillin for the treatment of caries. Under an external magnetic field, the iron oxide-encapsulating polymersomes (IOPs) could penetrate deeper in the biofilms, promoting the delivery of the antibiotics. Thus, the IOPs were able to generate ROS *via* the encapsulated nanozymes and released antibiotics in a 20 μm thick *Staphylococcus epidermidis* biofilm (Fig. 5A). Confocal laser scanning microscopy analysis results shown in Fig. 5B demonstrated that 40 μg mL^{-1} SPION and 20 μg mL^{-1} of methicillin containing IOPs could achieve complete eradication of methicillin-resistant *S. epidermidis* biofilms, the main cause of dental caries.[44]

In addition to the oxidoreductase mimics for combating the biofilms, nanomaterials with hydrolase-like property can also serve as antibiofilm agents. In the growth process of bio-

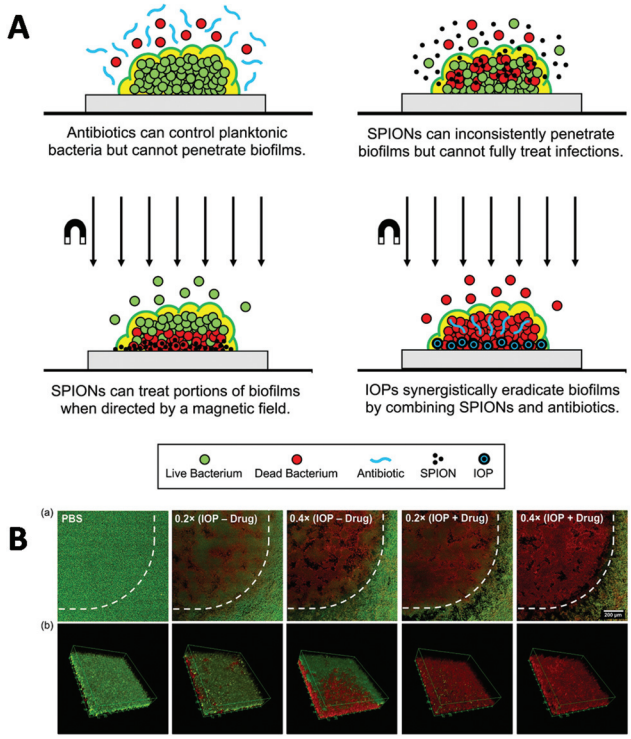


Fig. 5 Antibacterial efficiency of IOPs. (A) Schematic of biofilm disruption treated with SPIONs with/without antimicrobials. (B) Anti-biofilm efficiency of IOPs. Laser scanning confocal microscopy images for LIVE (green)/DEAD (red) staining of biofilms under different treatments for 24 h (1 × stock = 100 mg mL^{-1} SPION; 50 mg mL^{-1} methicillin). (a) Living and dead bacteria in the boundary of the external applied magnetic field for different treatments from tile scans collected halfway across the biofilm. (b) 3D reconstructions of *z*-stacks collected across the biofilm thickness inside the magnetic field. Reprinted with permission from ref. 44. Copyright Elsevier 2017.

films, eDNA plays a significant role in the interaction between the cells and their adhesion to the surface. Also, it is closely related to the formation of structural stability, the guidance of bacterial motility, and the resistance to antibiotics.[64,65] Accordingly, eliminating eDNA is likely to be a promising method for disrupting the biofilm. DNase is a kind of enzyme capable of disposing off eDNA.[66] However, the limited penetrating ability and operational stability impede its further application. It is well known that Ce(IV)-containing biocatalysts can serve as DNase mimics to hydrolyze DNA or RNA. Qu and colleagues successfully synthesized DNase-mimetic artificial enzyme (DMAE) by assembling cerium(IV) ion complexes on the Au component of the Fe_3O_4/SiO_2 core/shell nanoparticles. The obtained DMAE showed efficient penetration and exhibited outstanding DNase-like property. It could induce the cleavage of 80% eDNA inside the biofilms and prevented over 90% of bacterial adhesion. Furthermore, DMAE was able to degrade eDNA in the established biofilms, consequently damaging the integrity of the established biofilms, which natural DNase could not match.[45] A recent study indicated that the marriage of two kinds of nanozymes could achieve complete biofilm elimination and the prevention of secondary biofilm formation. In this study, Au-doped MIL-88B (Fe) (named as MOF_{-Au}) was first prepared to exert peroxidase-like activity. On adjusting the dosage of Au to 2.5 μmol, the obtained $MOF_{-2.5Au}$ could achieve the highest peroxidase-like activity. Ce complexes were then modified on the surface of the prepared $MOF_{-2.5Au}$ to provide DNase-like activity. In this way, the obtained $MOF_{-2.5Au-Ce}$ could possess both peroxidase- and DNase-like activity. The antibacterial treatment and mouse wound model demonstrated that $MOF_{-2.5Au-Ce}$ alone could only disperse the biofilms, while the combined system of both $MOF_{-2.5Au-Ce}$–H_2O_2 could destroy most of the biofilms. Compared with the $MOF_{-2.5Au}/H_2O_2$ mixture system, $MOF_{-2.5Au-Ce}$–H_2O_2 caused more severe loss of biomass. These outcomes confirmed the idea that the integrated nanozymes ($MOF_{-2.5Au-Ce}$) were able to disperse the biofilms *via* DNase-mimic activity and simultaneously killed the exposed bacteria by ROS.[46] This work can provide a creative way to enhance the anti-biofilm efficacy by a nanozyme-based synergistic system.

Furthermore, nanomaterials with haloperoxidase-like activity could also be used for anti-biofilm activity through interfering quorum sensing. Quorum sensing is a cell-to-cell communication process that helps a bacterial community to regulate the gene expression in response to cell density changes. Bacteria exchange information through quorum sensing, thus eliciting a series of physiological activities to build an advanced organism. Quorum sensing relies highly on chemical signal molecules, namely, autoinducers, which deliver information on the cell density changes. Quenching these signaling compounds can seriously interfere with quorum sensing, which consequently inhibits the formation of biofilm. Haloperoxidase has been proved to have the ability to catalyze the synthesis of antagonists against the autoinducers to disrupt QS.[67,68] Inspired by this, Tremel *et al.* discovered that CeO_{2-x} nanorods exhibited intrinsic haloperoxidase-like capacity and could be used for combating biofilms. In the presence of Br^- and H_2O_2, the CeO_{2-x} nanorods could catalyze the production of HOBr. The generated HOBr was destructive for the biofilms. They interpreted that the CeO_{2-x} nanorods containing both tri- and tetravalent states of cerium could form a polycrystalline construction. This mixed-valence state might contribute to rapid redox cycles, which correlated closely with the catalytic activity. To verify the potential application of the CeO_{2-x} nanorods, a plate coated with a CeO_{2-x} nanorod-containing paint was designed. The control experiment demonstrated that the CeO_{2-x}-treated plate showed little indication of biofouling.[47] Similarly, CeO_{2-x} nanorods could be used in nanofibers to prevent biofilm formation. A study showed that electrospun PVA mats containing the CeO_{2-x} nanorods showed haloperoxidase-like activity and high anti-biofouling properties.[69]

Summary and outlook

In this review, we summarized the recent progress of nanozymes for antibacterial/antibiofilm applications. The catalytic

activities, such as enzyme-like activities of peroxidase, oxidase, DNase, and haloperoxidase, of nanozymes can cause irreversible damage to bacteria/biofilms. These nanozymes as antimicrobial agents have a host of advantages including low cost, high stability, easy functionalization, and other attractive optical, electronic, and magnetic properties. However, there are still several problems that need to be addressed for the further development of nanozymes and their antimicrobial applications.

(1) Although nanozymes can overcome some shortcomings of natural enzymes, their catalytic activities cannot keep up with that of the natural enzymes. Moreover, nanozymes usually have a low binding affinity for the substrate. Therefore, the exploration of highly efficient nanozymes with excellent substrate affinity is urgently needed. An effective way is to further optimize their size, morphology, component as well as surface modification. For instance, through surface functionalization,[70] we can mimic the surface microenvironment of the natural enzymes and thus obtain better affinity towards the substrates. Alternatively, the design of novel nanozymes provides an additional way to construct highly efficient antimicrobial agents. To date, the focus has been on redox nanozymes. The introduction of new nanozymes, especially new types of nanozymes (*e.g.*, proteolytic enzyme), might provide unexpected antimicrobial activities.

(2) Although nanomaterials possess many attractive optical, electronic, and magnetic properties, these properties have not been utilized. By integrating these special physicochemical properties, unique systems may be constructed.

(3) Previous studies have shown that many nanomaterials can simultaneously possess multi-enzyme-like properties; however, whether these enzymatic activities will interfere with each other is unclear. For instance, gold nanoparticles have peroxidase, superoxide dismutase and catalase mimicking activities. The presence of the superoxide dismutase- and catalase-like activities might affect the overall antimicrobial performance of nanomaterials.[71,72] Therefore, researchers need to pay more attention to these issues.

(4) Plenty of nanozymes have been discovered to have the capability of killing bacteria and inhibiting biofilm formation. However, the detailed mechanisms are still unclear.

(5) For exploring the practical applications of nanozymes *in vivo*, the long-term biosafety of nanozymes should be considered in the future as most of the toxicity examinations reported to date have been performed on mice for a short period of time. Moreover, whether a hidden safety risk exists should be paid more attention to in the future.

Due to the rapid advancement in nanotechnology and the enormous achievements in bio- and biomimetic applications, we expect that this active research area will continue to thrive and mature in the future.

Conflicts of interest

There are no conflicts to declare.

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